PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/535 — A1

(11) International Publication Number: **WO 00/18405**

(43) International Publication Date: 6 April 2000 (06.04.00)

(21) International Application Number: PCT/GB98/02895

(22) International Filing Date: 25 September 1998 (25.09.98)

(71) Applicant *(for all designated States except US)*: PHARMAGENE LABORATORIES LTD. [GB/GB]; 2A Orchard Road, Royston, Hertfordshire SG8 5HD (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BAXTER, Gordon, Smith [GB/GB]; Pharmagene Laboratories Ltd., 2A Orchard Road, Royston, Hertfordshire SG8 5HD (GB). COLEMAN, Robert, Alexander [GB/GB]; Pharmagene Laboratories Ltd., 2A Orchard Road, Royston, Hertfordshire SG8 5HD (GB). TILFORD, Nicholas [GB/GB]; Pharmagene Laboratories Ltd., 2A Orchard Road, Royston, Hertfordshire SG8 5HD (GB).

(74) Agents: WHITAKER, Iain, Mark et al.; Sommerville & Rushton, Business Link Building, 45 Grosvenor Road, St. Albans, Hertfordshire AL1 3AW (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: USE OF PROSTANOID ANTAGONISTS FOR THE TREATMENT OF PRIMARY HEADACHE DISORDERS

(57) **Abstract**

The present invention relates to the use of EP_4 antagonists in the treatment of primary headache disorders and drug–induced headaches and in the preparation of medicaments for the treatment of primary headache disorders and drug–induced headaches. A new use for AH22921 and AH23848 is described.

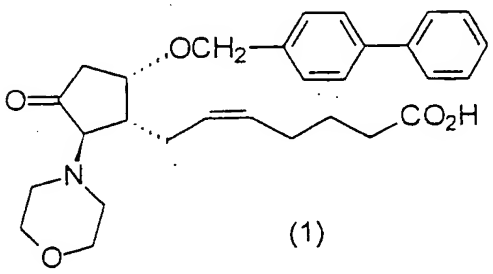
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

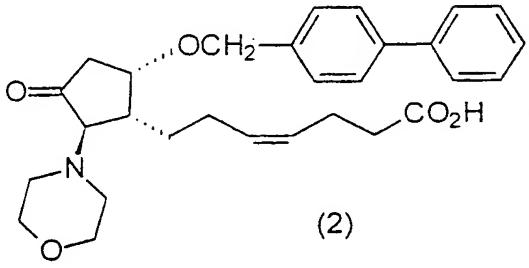
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

USE OF PROSTANOID ANTAGONISTS FOR THE TREATMENT OF PRIMARY HEADACHE DISORDERS

The present invention relates to a method of treatment of primary headache disorders and drug-induced headaches in humans and other mammals and to the use of compounds in the preparation of a medicament for the treatment of primary headache disorders and drug-induced headaches. In particular, this invention relates to a new medical use for compounds which act as antagonists at prostanoid EP_4 receptors and pharmaceutical compositions containing them. Two such EP_4 receptor antagonists are AH22921(1) and AH23848(2).



(1)



(2)

It has unexpectedly been discovered that EP_4 antagonists can alleviate the headache symptoms of primary headache disorders such as migraine. As used herein the term "primary headache disorder" includes migraine, tension-type headache, cluster headache, analgesic rebound headache, chronic paroxysmal hemicrania and headache associated with vascular disorders. Accordingly, the present invention, in a first aspect, provides a method of treatment of primary headache disorders and drug induced headaches in humans and other mammals, which method comprises administering an effective amount of an EP_4 antagonist or a pharmaceutically acceptable salt and/or solvate thereof.

There is also provided, according to a further aspect, the use of an EP_4 antagonist in the preparation of a medicament for use in the treatment of primary headache disorders and drug-induced headaches.

In any of the above aspects of the invention the EP_4 antagonist may be prostanoid or non-prostanoid in type. The invention is intended to encompass all known EP_4 antagonists and those yet to be discovered.

In a presently preferred aspect the invention provides for the use of AH22921(1) or AH23848(2) or pharmaceutically acceptable salts and/or solvates thereof in the preparation of a medicament for the use in the treatment of primary headache disorders or drug induced headaches.

In a further aspect of the present invention EP_4 antagonists may, if desired, be used in combination with one or more other therapeutic agents such as an ergot derivative, for example dihydroergotamine, a 5-HT_2 antagonist, for example ketanserin, or a 5-HT_{1D} agonist, for example sumatriptan, naratriptan or zolmitriptan, or a β-blocker for example propranolol.

There is a widely held view that the pain of migraine headache originates from abnormally distended blood vessels in the cerebral vasculature. Dilatation in cerebral blood vessels, would cause local pressure resulting in the activation of local sensory pathways and pain. This is the case also for the other aforementioned primary headache disorders and drug-induced headaches.

Many drugs are used to treat primary headache disorders such as migraine including NSAIDS, ergot alkaloids, and several compounds that interact with different subtypes of 5-hydroxytryptamine (5-HT) receptors either as agonists (e.g. sumatriptan) or antagonists (e.g. ketanserin). However, of the drugs that interact with 5-HT receptors only the class of compounds described as 5-HT_{1D} agonists, of which

sumatriptan is an example, will relieve an established headache. 5-HT_{1D} agonists are well known to cause vasoconstriction in the cerebral vasculature which supports the vasodilatation theory [Humphrey, P.P.A., Feniuk, W., Motevalian, M., Parsons A.A. and Whalley, E.T., 'The vasoconstrictor action of sumatriptan on human dura mater' in 'Serotonin: Molecular Biology, Receptors and Functional effects' ed. Fozard, J. and Saxena, P.R., Birkhauser Verlag, Basel, 1991].

Exogenous administration of the potent vasodilator E-series, but not I-series, prostanoids to migraineurs is known to induce migraine-like symptoms [Carlson, L.A., Ekelund, L.G. and Oro, L. (1986) Acta Med. Scand. 183, 423; Peatfield, R. (1981) Headache 32, 98-100]. This evidence, together with the effectiveness of NSAIDS (which act by inhibiting the biosynthesis of prostanoids) in both preventing or relieving a migraine attack [Karachalios, G.N., Fotiadou, A., Chrisikos, N., Karabetsos, A. and Kehagoiglou (1992) Headache 21,190; Hansen, P. (1994) Pharmacol. Toxicol. 75, Suppl.2, 81-82] supports the involvement of prostanoids in the aetiology of the disease. The precise role of prostanoids is unclear but could involve a combination of local vasodilator, inflammatory, or hyperalgesic actions. The prostanoid most often associated with such actions is PGE_2.

We have examined the action of a number of prostanoids on human isolated cerebral blood vessels and made the unexpected discovery that PGE_2 has a complex action on these vessels whereas the other vasodilator prostanoids, PGD_2 and PGF_{2a}, produce no effects. PGE_2 causes constriction of larger vessels (>than 1mm diameter), but more significantly we believe, in the context of pain associated with migraine, it surprisingly causes a potent concentration-related relaxation of smaller cerebral vessels (<1mm diameter). By studying a variety of pharmacologically active agents this relaxant effect was found to be mediated by prostanoid EP_4 receptors.

We believe this unexpected action of PGE_2 could account for the pain in migraine and that a selective EP_4 antagonist would be a novel and effective anti-migraine agent with advantages over existing therapies, especially NSAIDS. As well as less side effect liability, an EP_4 antagonist should exhibit greater efficacy than an NSAID because an NSAID would eliminate both the detrimental vasodilator and beneficial vasoconstrictor effects on cerebral vasculature caused by endogenous prostaglandins. In contrast, an EP_4 antagonist should only inhibit the detrimental vasodilator effect.

A further embodiment of the invention is the combination of an EP_4 receptor antagonist with other therapeutic agents used in the treatment of migraine for example, with an ergot derivative (e.g. dihydroergotamine), a 5-HT_2 antagonist (e.g. ketanserin), or a 5-HT_{1D} agonist (e.g. sumatriptan, naratriptan or zolmitriptan) or a β-blocker (e.g. propranolol).

Thromboxane A_2 (TXA_2), an active metabolite of arachidonic acid in human platelets, is a potent constrictor of vascular smooth muscle and aggregator of platelets. AH22191(1), AH23848(2) and related compounds antagonise the actions of TXA_2 and therefore inhibit platelet aggregation and bronchoconstriction. Hence these compounds have been claimed for use in the treatment of asthma and as anti-thrombotic agents in cardiovascular disorders (GB Patent 2, 028, 805 and US Patent 4, 342, 756 describe AH22191 and AH23848, respectively). Additionally, both AH22191 and AH23848 have also been shown to be weak antagonists of PGE_2-induced relaxation of piglet saphenous vein (pA_2 values 5.3 and 5.4, respectively) through blockade of EP_4 receptors [Coleman, R.A., Grix, S.P., Head, S.A., Louttit, J.B., Mallett, A. and Sheldrick, R.L.G. (1994) Prostaglandins 47, 151-168; Coleman, R.A., Mallett, A. and Sheldrick, R.L.G. (1995) Advances in Prostaglandin,

Thromboxane and Leukotriene Research, 23, 241-246] but have no effect on the other EP receptor subtypes EP_1, EP_2 and EP_3. However, we have now shown that AH23848 is an antagonist of the relaxant effect of PGE_2 on human cerebral vessels. AH23848 shows similar EP_4 antagonist potency on human isolated cerebral arteries as it does on piglet saphenous vein. Thus, EP_4 receptor antagonists as a class, and AH22191 and AH23848 in particular, should be effective in the treatment of migraine.

A method of identifying and quantifying EP_4 receptor antagonists is described in the two publications by Coleman, R.A. listed above. The entire text of these publications is hereby imported by reference and forms an integral part of this disclosure and the inventive concepts described.

The characterisation of EP_4 receptors is also discussed in the review by Coleman R. A. et al [Coleman R. A. et al Eicosanoids: From Biotechnology to Therapeutic Applications, Folco, Samuelsson, Maclouf, and Velo, eds., Plenum Press, New York, 1996, p137-154], the text of which is also imported herein by reference and forms an integral part of this disclosure.

For the avoidance of doubt, in the context of this invention, an EP_4 receptor antagonist is any compound, agent or mixture showing antagonist activity at EP_4 receptors using the methodology set out above, including and especially antagonist activity against PGE_2 induced relaxation of human isolated cerebral blood vessels.

The EP_4 antagonists may be administered as the raw chemical but the active ingredients are preferably presented as a pharmaceutical formulation. Suitable pharmaceutical formulations are described in the above referenced patent specifications.

Thus, the EP_4 antagonists may be formulated for oral, buccal, parenteral, topical, depot or rectal administration or in a form suitable for administration by

inhalation or insufflation (either through the mouth or nose). Oral and parenteral formulations are preferred.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia; non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxbenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The EP_4 antagonists may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in

unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The EP_4 antagonists may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The EP_4 antagonists may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The EP_4 antagonists may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion

exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the EP_4 antagonists may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

Suitable dose ranges may be calculated by those skilled in the art in light of toxicological data. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient, and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected. A suitable dose range is for example 0.1mg/kg to about 400mg/kg bodyweight per day.

CLAIMS

1. The use of an EP_4 antagonist in the preparation of a medicament for use in the treatment of a primary headache disorder or drug-induced headache

2. The use according to claim 1 wherein the EP_4 antagonist is a prostanoid-type antagonist.

3. The use according to claim 1 wherein the EP_4 antagonist is a non-prostanoid-type antagonist.

4. The use according to claim 1 or claim 2 wherein the EP_4 antagonist is AH22921(1) or AH23848(2) or pharmaceutically acceptable salts or solvates thereof.

5. The use according to any preceding claim wherein the EP_4 antagonist is combined with one or more therapeutic agents selected from an ergot derivative, a 5-HT_2 antagonist, a 5-HT_{1D} agonist, or a β-blocker.

6. The use according to claim 5 wherein the ergot derivative is dihydroergotamine.

7. The use according to claim 5 wherein the 5-HT_2 antagonist is ketanserin.

8. The use according to claim 5 wherein the 5-HT_{1D} agonist is selected from sumatriptan, naratriptan or zolmitriptan.

9. The use according to claim 5 wherein the β-blocker is propranolol.

10. The use of an EP_4 antagonist substantially as herein described.

11. A method of treatment of a primary headache disorder or drug-induced headache in a human or other mammal comprising administering a therapeutically effective amount of an EP_4 antagonist or a pharmaceutically effective salt and or solvate thereof.

12. A method of treatment as claimed in claim 11 wherein the EP_4 antagonist is a prostanoid-type antagonist.

13. A method of treatment as claimed in claim 11 wherein the EP_4 antagonist is a non-prostanoid-type antagonist.

14. A method of treatment as claimed in claim 11 wherein the EP_4 antagonist is AH22921(1) or AH23848(2) or pharmaceutically acceptable salts or solvates thereof.

15. A method of treatment as claimed in claim 11 wherein the EP_4 antagonist is combined with one or more therapeutic agents selected from an ergot derivative, a 5-HT_2 antagonist, a 5-HT_{1D} agonist, or a β-blocker.

16. A method of treatment as claimed in claim 15 wherein the ergot derivative is dihydroergotamine.

17. A method of treatment as claimed in claim 15 wherein the 5-HT_2 antagonist is ketanserin.

18. A method of treatment as claimed in claim 15 wherein the 5-HT_{1D} agonist is selected from sumatriptan, naratriptan or zolmitriptan.

19. A method of treatment as claimed in claim 15 wherein the β-blocker is propranolol.

INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/GB 98/02895

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A.A. PARSONS ET AL.: "Effects of prostanoids on human and rabbit basilar arteries precontracted in vitro." CEPHALAGIA, vol. 9, no. 3, 1989, pages 165-171, XP002086056 see the whole document -----	1-4, 11-14

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 November 1998	11/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Klaver, T

1